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Review

# Personalized plasma-based medicine to treat age-related diseases

Eduardo Anitua [a,b,*], María Troya [b], Mar Zalduendo [b], Gorka Orive [a,c,d,*]

[a] Eduardo Anitua Foundation for Biomedical Research, Vitoria, Spain
[b] BTI-Biotechnology Institute, Vitoria, Spain
[c] NanoBioCel Group, Laboratory of Pharmaceutics, University of the Basque Country, School of Pharmacy, Vitoria, Spain
[d] Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Vitoria, Spain

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ABSTRACT

As social and health needs are changing, new challenges to develop innovative alternatives arise to address unmet medical needs. Personalized medicine is emerging as a promising and appealing therapeutic option. The use of patient's own plasma and platelets as therapeutics is providing new avenues in the treatment of acute and chronic tissue injuries by promoting tissue repair and regeneration. Plasma and platelet-based therapies mimic the physiological repair process by releasing autologous growth factors and creating a natural, biodegradable and transient scaffold that acts as transient matrix. This review summarizes the recent advances and challenges in the field of personalized plasma-based medicine and its potential to treat age-related diseases.



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## 1. Introduction

The global aging of the population is increasing at an accelerating rate. These demographic changes are leading to an increased prevalence of age-related degeneration and chronic diseases. Traditional medicine is trying to solve all these problems. In fact, successful organ transplantation (allografts) is considered among one of the major milestones of medicine of the last decades. However, success of transplantation is limited by shortage in the supply of transplantable organs and by the potential organ rejection.

As social and health needs are changing, the pressure to develop new alternatives, designed to address unmet medical needs, increases. Over the last years, the gradual understanding of the biological processes involved in wound healing has paved the way for developing new regenerative therapies with the ultimate goal of promoting and accelerating tissue regeneration [1,2]. In this context, personalized medicine is emerging as a promising and appealing therapeutic option. It is based in the complex uniqueness of each patient offering a tailor-made treatment for improving the management of patients [1,3]. Already in

* Corresponding authors at: Eduardo Anitua Foundation for Biomedical Research, Jacinto Quincoces, 39, Vitoria 01007, Álava, Spain.
*E-mail addresses:* eduardoanitua@eduardoanoitua.com (E. Anitua), gorka.orive@bti-implant.es (G. Orive).

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ancient Greece, the father of medicine, Hippocrates, mentioned the importance of personalizing the medicine: "*it is more important to know what sort of person has a disease than to know what sort of disease a person has*".

Autologous plasma-based therapies may be a form of personalized medicine. These therapies employ human-based cells or tissues, may or not manipulate them outside the body, and reintroduce them into the same donor [4]. This emerging field, by being autologous, provides new advantages in the clinical setting: (i) the donor is immediately available, (ii) no immunosuppression is required, (iii) no rejection occurs, (iv) elimination of graft versus host disease, (v) risks associated to disease transmission are eliminated and (vi) in general, does not present ethical conflicts [5].

Platelet rich plasma is included within these types of autologous therapies. It is based on properly selecting, from human blood, a pool of cells and growth factors, together with fibrin forming proteins to create a three-dimensional (3D) scaffold, necessary to support tissue regeneration. As derived from patient's own blood, platelet rich plasma is an affordable and minimally invasive technique [2].

In this review we describe the potential of plasma-based medicine and in particular platelet rich plasma as an autologous therapy. We provide insight about their biological effects as well as some pivotal preclinical and clinical applications.

## 2. Mimicking the healing process

Following any tissue injury, one of the main priorities of the organism is the restoration of tissue integrity and function. For this purpose, the process of wound healing goes through a sequence of continuous, overlapping and precisely programmed phases involving rapid hemostasis, controlled inflammation, cell migration to the injury site and subsequent cell proliferation and differentiation, and finally, formation and remodeling of extracellular matrix (ECM) [6–8]. During the healing process some remarkable events must be specially mentioned.

### 2.1. Fibrin scaffold

Polymerized fibrin that is structured from soluble fibrinogen, is the principal component of blood clots, and provides a provisional scaffold which enables formation of a temporary matrix in the wound bed. Fibrinogen is a key protein for both hemostasis and homeostasis. In fact, fibrinogen assembles into the ECM at sites of tissue damage, where it may be involved in cell type-specific mechanisms of wound repair [9]. Its contribution largely depends on the interactions between specific-binding sites on fibrin(ogen), pro-enzymes, clotting factors, enzyme inhibitors, and cell receptors as well as on the structural composition of fibrin [10]. Fibrinogen circulates in normal human plasma in a high and low molecular weight form (HMW and LMW, respectively). This fibrinogen heterogeneity strongly influences coagulation rate, fibrin structure and endothelial cell behavior. HMW fibrin matrices display a porous and malleable network with thicker fibers whereas the thinner fibers bundles of LMW fibrin matrix form a dense structure. Moreover, HMW fibrins stimulate endothelial cell proliferation and tube formation more than LMW matrices do. These differences could be exploited for therapeutic applications [11,12].

### 2.2. Growth factors

The aggregated platelets, which are trapped in the provisional fibrin matrix, release multiple growth factors that exert outstanding roles in modulating the inflammatory stage and cell recruitment to the damaged area (Table 1). In addition, these bioactive molecules are key regulators of the main tissue regenerative processes such as cell migration, proliferation, differentiation, angiogenesis and ECM biosynthesis. Growth factors modulate their effects through binding to specific receptors on the target cell surface. Following this binding, signal-transduction pathway involves a complex array of events such as second messengers, protein phosphorylation, gene expression and protein synthesis [13]. Multiple growth factors may share mechanisms while the same growth factor may deliver different messages depending on the cell and receptor type they bind to.

### 2.3. The active role of cells

After hemostasis and inflammatory stages, damaged tissue restoration process is intensified. This process is carried out by several phenotypes through different procedures. Tissue-specific adult stem cells gain special importance in the response to regulatory signals from the injured tissue [27]. In addition, bone marrow-derived stem cells significantly contribute to tissue regeneration by providing trophic factors that modulate the local environment and by promoting angiogenesis, reepithelialization and granulation tissue formation [28]. Stem cell behavior is profoundly modulated by different signals such as cell-cell interactions and the ECM, components all of them of the stem cell niche, a dynamic structure that includes immune cells during inflammation and wound healing process [29]. It is also necessary to mention the role of macrophages during the inflammatory response and tissue repair. Considered more than immune cells, macrophages have the ability of acquiring distinct functional phenotypes in response to the microenvironmental cues. Traditionally, two main phenotypes have been identified: the classically activated macrophages (M1) that produce many inflammatory cytokines, reactive oxygen species and nitrogen intermediates and the alternatively activated macrophages (M2) that are characterized by low levels of pro-inflammatory cytokines and high IL-10 expression. M1 supports pathogen killing and drives the inflammatory response whereas M2 sustains tissue remodeling. Both phenotypes also differ in the metabolic pathway, since glycolytic pathway is involved in M1 polarization, whereas fatty acid oxidation occurs in M2. Macrophages show different activation states, therefore, a continuum of phenotypes is expected to occur at the wound site. This macrophage plasticity suggests a complex molecular system that enables them to play multiple roles in inflammation and regeneration [30–32].

**Table 1**
Main growth factors involved in human tissue regeneration [24–26].

| Growth factor | Molecular weight (kDa) | Types | Receptors | Mechanisms of activation and signaling | Main function |
|---|---|---|---|---|---|
| EGF [14,15] | 6.4 | – | EGFR (ErbB1) | Receptor tyrosine kinases | Cell growth, proliferation, differentiation and survival. |
| FGF [16,17] | 7–38 | FGF1-14, FGF16-23 | FGFR1, FGFR2, FGFR3, FGFR4 | Receptor tyrosine kinases | Cell proliferation, migration, differentiation, angiogenesis and survival. |
| PDGF [18,19] | 32–35 | -AA, -BB, -AB, -CC, -DD | PDGF-α and PDGF-β | Receptor tyrosine kinases | Chemotactic, cell proliferation and extracellular matrix production. |
| TGF-β [20,21] | 25 | -β1, -β2, -β3 | TGFβRI and TGFβRII | Serine/threonine kinase receptors. | Wound healing, angiogenesis and immune suppression promotion. Differentiation. Extracellular matrix production, and wound contraction. |
| VEGF [22,23] | 34–42 | -A, -B, -C, -D and placental growth factor | VEGFR-1, VEGFR-2 and VEGFR-3. Neuropilins (Nrp-1 and Nrp-2). | Receptor tyrosine kinases. Receptors for semaphorins. | Endothelial cell proliferation and migration. |